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Acute Coronary Syndromes

A SPECIFIC ANTIDOTE FOR TICAGRELOR

Poster Contributions
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Background: A Fab, MEDI2452, is being developed as an antidote for ticagrelor patients requiring urgent surgery or experiencing major or life-threatening bleeding where ticagrelor reversal may be desirable.

Methods: MEDI2452 was isolated and optimized by human antibody phage display. The affinity was measured by KinExA and selectivity was determined by competition binding. Potency to reverse ticagrelor or its active metabolite (TAM) mediated inhibition of ADP induced platelet aggregation was determined *in vitro* in human platelet rich plasma. Plasma unbound fraction of ticagrelor was determined in parallel by equilibrium dialysis. The speed of onset and the extent of MEDI2452 mediated reversal of anti-platelet effect were determined *ex vivo* after intravenous (*i.v.)* dosing of ticagrelor. Just after termination of ticagrelor infusion, at an average plasma exposure of 1.4 μM, mice were given an *i.v.* bolus of 250 mg/kg MEDI2452. At 5, 30 and 60 min post MEDI2452 administration blood samples were collected for ADP-induced whole blood aggregometry and plasma exposure.

Results: MEDI2452 has an affinity for ticagrelor and TAM of 20 pM with no significant binding to adenosine, ADP, ATP or any structurally related compounds. The specificity of MEDI2452 for ticagrelor and TAM was supported by a crystal structure of the Fab-Hapten complex. MEDI2452 produced a concentration-dependent reversal of 1 μM ticagrelor and TAM mediated inhibition of platelet aggregation with mean IC_{50} values of 0.64 and 0.78 μM, respectively. The recovery of platelet aggregation occurred in parallel with a reduction in plasma unbound ticagrelor with mean IC_{50} value of 0.49 μM. In mice, ticagrelor treatment inhibited ADP induced aggregation by ≥97%. MEDI2452 reversed the aggregation response by 34, 94 and 83% at 5, 30 and 60min, respectively.

Conclusion: MEDI2452 1) Specifically binds to ticagrelor and TAM with high affinity, 2) Concentration dependently neutralizes the plasma unbound fraction of ticagrelor and reverses ticagrelor and TAM mediated inhibition of platelet aggregation *in vitro* and 3) Rapidly and effectively reverses platelet aggregation when given to ticagrelor treated mice.